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Original

Clinical Study of the Efficacy and Safety of Liposomal Amphotericin B for the Treatment of Fungal Infections in Non-neutropenic Patients

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Abstract: Liposomal amphotericin B (L-AMB) is reported in Japan to be less effective and not as safe for treating severe fungal infections in non-neutropenic patients as in neutropenic patients. Therefore, we evaluated the clinical efficacy and safety of L-AMB as an antifungal agent in non-neutropenic patients. The efficacy of L-AMB administered intravenously in patients with severe fungal infections was retrospectively investigated by reviewing medical records from November 2007 to July 2010. The records of 18 eligible adult patients were analyzed according to the L-AMB dose they received: standard (2.5 mg / kg / day; n＝5) and high (＞2.5 mg / kg / day; n＝13). The average age of the standard- and high-dosage group was 71.4 and 60.3 years, respectively. The 30-day survival rate in the standard- and high-dosage group was 20% (n＝1) and 76.9% (n＝10), respectively ($P＝0.047$). A significant antipyretic effect was observed in the high-dosage group ($P＝0.001$). There was no relationship between the dosage of L-AMB and any side effect. By carrying out the treatment according to the information provided at the time of administration, no cases were discontinued because of side effects. A high dosage of L-AMB is more effective than the standard dosage and both dosages are well-tolerated in non-neutropenic patients.

Key words: Liposomal amphotericin B (L-AMB), high dosage, safety, fungal infection

Introduction

Recent medical and pharmaceutical developments have allowed medications to be administered to many patients with severe immunosuppression due to life-threatening conditions. However, despite an overall decrease in the mortality rate of patients with visceral mycoses from 4.5% in 1989 to 3.7% in 1993, the mortality rate thereafter showed an increasing trend, reaching 4.6%

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in 2001[1]. In particular, the mortality rate of deep mycoses ranges from 40%–60% in patients with a very poor prognosis. Such situations lead to increased healthcare costs. Candidiasis is the most common deep mycosis encountered in emergency rooms and intensive care units. The risk factors of candidemia include indwelling central venous catheters, total parenteral nutrition, and antimicrobial administration preceding long-term administration of broad-spectrum antibiotics, especially for burns, dialysis, ventilators, and treatment of fungal colonization[2].

For candidemia in patients with normal neutrophil levels, *Candida albicans* is the most insensitive to eradication, and fosfluconazole is the first choice for treatment. Meanwhile, micafungin is preferable for patients pretreated with azole-derived antifungal agents or fosfluconazole for *Candida glabrata* or *Candida krusei* infections[2]. The prevalence of non-*C. albicans* infections involving species in addition to the two mentioned above is increasing[3,4]. The minimum inhibitory concentrations of both micafungin and fosfluconazole for candidemia with non-*C. albicans* are also tending to increase[3]. Although liposomal amphotericin B (L-AMB) is fully effective for these types of candidemia with little resistance, it incurs a greater medical expense due to increased rates of acute renal failure and mortality[5]. Amphotericin B at dosages exceeding 35 mg / day is a risk factor for nephrotoxicity ; gender, body weight of more than 90 kg, and chronic renal disease are also risk factors. Moreover, concurrent administration of amikacin or cyclosporine confers a risk of acute renal failure ; therefore, amphotericin B cannot be safely administered to patients taking these drugs, making treatment difficult in severe cases[6,7]. The development of a drug-delivery system to administer L-AMB, aimed at reducing side effects, has demonstrated efficacy[8]. Therefore, L-AMB is a potential key drug for the treatment of serious fungal infectious diseases. Indeed, the effectiveness of L-AMB as well as conventional amphotericin B as an empirical antifungal therapy has been demonstrated in patients with febrile neutropenia[9].

Daily doses of L-AMB usually range from 2.5～5 mg / kg for fungal infectious diseases except cryptococcal meningitis[10]. However, in Japan, L-AMB is restricted for use in blood disorders as a standard therapy[11,12]. L-AMB therapy is recommended for candidal infections in non-neutropenic adult patients in whom indwelling catheters cannot be removed[13]. The presence of a central venous catheter is reported to be an independent predictor of biofilm-forming candidal bloodstream infection, and L-AMB therapy is highly effective in such patients[14].

In our hospital, L-AMB is administered at high dosages for all severe fungal infections with the aim of improving survival rates. Therefore, the present study retrospectively evaluated the clinical effectiveness of L-AMB at a high dose rate. The ultimate goal of this study was to improve safety during high-dosage L-AMB administration and provide invaluable information for Infection Control Team (ICT) pharmacists.

Material and methods

Recommendations of the ICT pharmacists

This study was approved by the Institutional Review Board of our institution. The pharmacist, who is part of the ICT, recommended the following for L-AMB administration : (1) infusion

should be performed over 2 hours (preferably 3 hours); (2) early potassium supplementation to prevent hypokalemia, which is very likely to occur 5～6 days after drug administration. If the serum potassium level is less than 3.0 mEq/l, administration of potassium formulations is recommended; (3) monitoring laboratory data including blood urea nitrogen (BUN), creatinine (Cre), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, γ-glutamyl transpeptidase, albumin, serum electrolytes (i.e., magnesium, potassium), and white blood cells (WBC); and (4) inspection of prescriptions and dissolution methods.

Medical record review

From November 2007 to July 2010, the medical records of 18 adult patients who received intravenous L-AMB at the recommendation of our hospital's ICT were retrieved. We classified the patients into two groups according to L-AMB dosage: 2.5 mg/kg/day (standard dosage) and $>$ 2.5 mg/kg/day (high dosage). Patients with blood disorders such as leukemia and febrile neutropenia with fungal infection were excluded from this study, because such patients may have been immunosuppressed. None of the patients were undergoing combination antifungal therapy.

Age, gender, weight, L-AMB dose, treatment duration, medicines other than L-AMB, and extracted laboratory data including WBC, C-reactive protein, AST, ALT, BUN, serum Cre, and β-D-glucan were recorded. Laboratory data from the start and end of L-AMB administration were compared. Thirty-day survival rates were also determined from the medical records.

Statistical analysis

Data are expressed as mean ± standard deviation. Patient background and 30-day survival rates were compared between the standard- and high-dosage groups. Univariate analyses were performed using the Wilcoxon rank–sum test and the χ^2 test. The level of significance was set at $P < 0.05$. All statistical analyses were performed with IBM SPSS 14.0J for Windows (IBM Corporation, Tokyo, Japan).

Results

Patient background

The mean L-AMB dosage of the standard- and high-dosage group was 2.5 ± 0.0 mg/kg/day ($n = 5$) and 4.7 ± 0.8 mg/kg/day ($n = 13$), respectively ($P = 0.001$; Table 1). The average age of the standard- and high-dosage group was 71.4 and 60.3 years, respectively ($P = 0.20$). Two patients in the standard-dosage group had candidemia and three had deep mycosis. In the high-dosage group, six patients had candidemia, 5 had deep mycosis, one had invasive pulmonary aspergillosis, and one had cryptococcosis. There was no clear association between surgery and fungal infection. Since autopsies were not performed after death, there was also no clear association between fungal infection and death. The duration of L-AMB administration was shorter in the standard-dosage group than in the high-dosage group, but no significant difference was observed.

Table 1. Patient characteristics in the standard- and high-dose liposomal amphotericin B groups

	Standard-dose group (n = 5)	High-dose group (n = 13)	*P* value
Average dosage (mg / kg / day)	2.5 ± 0.0	4.7 ± 0.8	< 0.01
Age (y)	71.4 ± 8.3	60.3 ± 18.8	0.20
Body weight (kg)	54.3 ± 9.8	50.2 ± 10.9	0.43
Sex (male)	3 (60%)	7 (53.8%)	1.00
Diabetes	2 (40%)	4 (30.7%)	1.00
Central intravenous catheter	3 (60%)	9 (69.2%)	1.00
History of surgery	0 (0%)	5 (38.5%)	0.25
Steroids	3 (60%)	3 (23.1%)	0.27
Antimicrobials	5 (100%)	13 (100%)	1.00
No. days until min. potassium	5.4 ± 2.3	6.0 ± 4.5	0.92
Hemodialysis	2 (40%)	6 (46.2%)	1.00
Previous antifungal therapy	3 (60%)	8 (61.5%)	1.00
No. days drug administered	7.8 ± 3.0	17.5 ± 16.8	0.35

Values are mean ± standard deviation, or number of cases (%).

Effectiveness

The 30-day survival rate in the standard- and high-dosage group was 20% (n = 1) and 76.9% (n = 10), respectively ($P = 0.047$). The antipyretic effect was significantly stronger in the high-dosage group.

Safety

Before L-AMB administration there were no significant differences between the standard- and high-dosage groups for total protein, albumin, WBC, β-D-glucan, AST, ALT, BUN, or potassium (Table 2). The WBC count as well as C-reactive protein and β-D-glucan levels tended to decrease in the high-dosage group after treatment. Mean serum potassium levels in the standard-dosage group decreased from 4.3 ± 0.9 to 3.9 ± 1.5 mEq / l, while in the high-dosage group values were 3.7 ± 0.6 and 4.0 ± 0.8 mEq / l, before and after treatment, respectively; neither change was significant.

Serum Cre levels increased significantly in both groups after treatment (Table 2). Three patients in the standard-dosage group and four patients in the high-dosage group had Cre levels above the normal range. In one patient, the Cre level was twice the normal value. In this particular patient, L-AMB was co-administered with a drug that causes renal insufficiency; as a result, the serum Cre level increased and the patient died. Therefore, factors other than L-AMB can increase serum Cre.

No infusion reactions or adverse events due to discontinuation were reported.

Table 2. Comparison of clinical laboratory values between standard- and high-dose liposomal amphotericin B groups

	Standard-dose group (n = 5)			High-dose group (n = 13)		
	Before	After	*P* value	Before	After	*P* value
TP (g / dl)	5.6 ± 1.1	5.2 ± 0.4	0.69	6.1 ± 1.1	6.2 ± 1.2	0.28
Alb (g / dl)	2.0 ± 0.6	1.9 ± 0.5	0.59	2.2 ± 0.5	2.3 ± 0.6	0.26
WBC ($\times 10^3$ / μl)	13.3 ± 7.8	15.9 ± 10.5	0.69	15.7 ± 8.3	13.1 ± 9.3	0.18
CRP (mg / dl)	10.1 ± 6.7	10.5 ± 10.1	0.89	11.0 ± 9.9	6.7 ± 4.6	0.08
Body temperature (°C)	38.7 ± 1.0	37.3 ± 0.6	0.07	38.1 ± 0.6	37.0 ± 0.4	< 0.01
β-D-glucan (pg / ml)[a]	405.0 ± 337.7	402.5 ± 342.1	0.42	302.2 ± 228.5	176.2 ± 165.8	0.12
AST (U / l)	89.8 ± 55.5	46.0 ± 27.7	0.23	44.7 ± 25.3	37.0 ± 23.5	0.42
ALT (U / l)	101.6 ± 97.2	61.2 ± 32.6	0.23	48.2 ± 40.2	42.7 ± 31.7	0.94
Cre (mg / dl)	2.1 ± 2.1	2.6 ± 1.9	0.04	2.0 ± 1.5	2.3 ± 1.7	0.03
BUN (mg / dl)	21.5 ± 15.1	42.6 ± 26.3	0.04	26.2 ± 12.9	33.3 ± 14.9	0.06
Potassium (mEq / l)	4.3 ± 0.9	3.9 ± 1.5	0.22	3.7 ± 0.6	4.0 ± 0.8	0.33

Values are mean ± standard deviation. [a] β-D-glucan ; standard-dosage group (n = 3) ; high-dosage group (n = 10). Abbreviations : TP, total protein ; Alb, albumin ; WBC, white blood cells ; CRP, C-reactive protein ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase ; Cre, creatinine ; BUN, blood urea nitrogen.

Discussion

In Japan, high-dose L-AMB is reported to have a lower safety and efficacy for treating severe fungal infections in non-neutropenic patients compared to neutropenic patients[15, 16]. However, the present study shows this treatment can be administered safely to such patients.

The superiority of L-AMB compared to voriconazole for the treatment of blood disorders with febrile neutropenia is clinically and economically recognized[17, 18]. The factors affecting survival and treatment success include catheter removal, APACHE II score, age, steroid use, and immunity[19]. Our study demonstrates the efficacy of L-AMB for patients with life-threatening *Candida* infection complicated with renal failure ; among all patients, 44% underwent additional hemodialysis. Serum Cre levels increased after treatment in some patients, although levels twice normal were only observed in one patient who eventually died. No renal insufficiency was observed in the high-dosage group when L-AMB was administered, highlighting the necessity of close monitoring.

Hamada *et al*[20] suggest events such as a decrease in serum potassium levels occur 5～6 days after the start of L-AMB treatment. Despite aggressive potassium administration 5～6 days after L-AMB administration, serum potassium levels reached a nadir, suggesting the need for periodical potassium administration in many cases. L-AMB (15 mg / kg / day) is tolerable in patients with *Aspergillus* infection, and no association between dosage and side effects has been reported[21]. Another prospective cohort study showed that the response rate to L-AMB (3 mg / kg / day) in patients with aspergillosis was 50%, while 10 mg / kg / day was not particularly useful. In addition, an L-AMB dosage of 10 mg / kg / day is reported to result in a higher rate of side effects[22]. In a domestic clinical trial[16], nearly all patients receiving the high dose exhibited

some kind of side effect.

Hypokalemia was not associated with renal or liver function in the present study, which is concordant with the results of a previous study[23]. In that study, L-AMB was administered at an average dose of 3.7 mg / kg and about half of the cases were treated with the drug as the first choice for severe invasive fungal infections in the intensive care unit with an efficacy of 40%[24]. We administered aggressive high doses for similar cases in the intensive care unit in accordance with the ICT recommendation that the dose should be infused over 3 hours. No infusion reactions occurred with this procedure, indicating that the ICT recommendations help avoid the side effects of high dosages.

Another study has reported that L-AMB becomes effective more than 8 days after administration ; therefore, continuous treatment is critical given that no adverse drug events occur[11]. Thus, the infusion rate is the key to preventing side effects.

Although the number of cases in the present study was very small, we aimed to clarify the efficacy of high doses of L-AMB at our institution. This study showed that a high dosage of L-AMB is suitable for treating non-neutropenic patients who cannot undergo catheter removal. We will continue to evaluate the safety and effectiveness of L-AMB treatment.

Conflict of interest disclosure

The authors have declared no conflicts of interest.

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